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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,493	02/27/2004	Susanne Leonhartsberger	LEONHARTSBERGER ET AL 1	8053

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EXAMINER	
RAMIREZ, DELIA M	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/26/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/789,493	LEONHARTSBERGER ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 8-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 8-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/18/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-4, 8-18 are pending.

Applicant's amendment of claims 1, 4, 11-18, cancellation of claims 5-7, and amendments to the specification as submitted in a communication filed on 12/18/2006 is acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 12/18/2006 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Objections

2. Claim 4 is objected to due to the recitation of "protein comprising the sequence SEQ ID NO: 1". For consistency with commonly used claim language, the claim should be amended to recite "protein comprising the sequence of SEQ ID NO: 1". Appropriate correction is required.

3. Claim 9 is objected to due to the recitation of "selected from the groups". This appears to be a typographical error. The claim should be amended to recite "selected from the group". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 2-3 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is necessitated by amendment.

6. Claims 2-3 are indefinite in the recitation of "wherein the bacterial strain used is a strain of the family *Enterobacteriaceae*" and "wherein the bacterial strain used is a strain of the genus *Escherichia*" because the bacterial strain recited in claim 1 is *E. coli*, which is a species of the family *Enterobacteriaceae* and of the genus *Escherichia.* Thus, claims 2-3 do not further limit the bacterial strain of claim 1. For examination purposes, it will be assumed that claims 2-3 are duplicates of claim 1. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. Claims 1-4 and 8-18 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

9. This rejection has been discussed at length in the Non Final action mailed on 9/26/2006 and is maintained for the reasons of record and those set forth below.

10. Applicant argues that claim 1 has been amended such that the bacterial strain is now limited to *E. coli*. Applicant submits that an enzyme is not necessarily defined by its structure and that an enzyme is defined by its activity. Applicant also submits that all enzymes of the same kind have the same enzymatic activity and catalyze the same reaction. According to applicant, the function and a test for determining the recited enzymatic activity is known in the art and described in the specification. Thus, it is

Applicant's contention that one of skill in the art should be able to produce an increased expression of any enzyme with SAM synthetase activity in an *E. coli* strain. With regard to the teachings of Witkowski et al. and Seffernick et al., Applicant asserts that these teachings are not relevant to the present invention as the enzymatic activity discussed in these references is not related to SAM synthetases.

11. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejections. Claims 1-3 and 8-18 as amended are directed to a method for the production of SAM wherein said method comprises (1) culturing an *E. coli* cell modified in any way such that SAM synthetase activity in said cell is increased by at least a factor of 2 compared to the unmodified *E. coli* cell, and (2) secreting SAM by said bacterial cell. Claim 4 is directed to the method of claim 1 with the added limitation that the SAM synthetase activity increased is that of a protein comprising SEQ ID NO: 1. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. The Examiner acknowledges that the claims are now limited to *E. coli* cells. However, the claims as written still encompass an extremely large genus of SAM synthetases, methods for increasing SAM synthetase activity in *E. coli* to the activity levels recited, and methods to obtain secretion of SAM which are unknown. It is noted that (1) enzymatically active SAM synthetases, (2) secretion of SAM, and (3) increase in SAM synthetase activity, are essential elements in the claimed invention. Therefore, for the claimed invention to be adequately described, the specification must adequately describe the essential parts of the invention.

While it is agreed that several SAM synthetases are known in the art, the claims require any enzymatically active SAM synthetase. Thus, the claims require not only those known in the art but also those which are unknown. It is reiterated herein that it is the amino acid sequence of a protein what determines the structural and functional properties of that protein. In the case of enzymes, such amino acid sequence determines the enzymatic activity of said enzyme. The specification fails to disclose (1) a structure/function correlation which would allow one of skill in the art to envision the structure of any

SAM synthetase as required by the claims, or (2) the critical structural elements which must be present in any protein to display SAM synthetase activity as recited. As indicated previously, the genus of SAM synthetases required encompasses enzymes which are structurally unrelated. The specification fails to provide a representative number of SAM synthetases defined by their amino acid sequence, or structural features common to members of the genus, which features constitute a substantial portion of the genus.

With regard to the teachings of Witkowski et al. and Seffernick et al., the Examiner acknowledges that these references do not specifically address SAM synthetases. However, these references are relevant to the issue at hand since they are clear examples of the unpredictability of the art with regard to how structural variability can alter function even when the structural variability is minimal. Thus, these references support the argument that the structures of those known SAM synthetases may not be sufficient to adequately described an entire genus of enzymes.

With regard to methods to increase the enzymatic activity of a protein to the levels recited, it is reiterated herein that the claims require unknown methods to increase SAM synthetase activity, such as (1) mutations in the coding region of a gene encoding the protein which would increase its enzymatic activity, (2) the presence of enhancers of that enzymatic activity which can be chemicals or the products of other genes, (3) mutations in the regulatory region of a gene encoding said protein, and (4) the presence of transcription enhancers which can be chemicals or the products of other genes. There is no description of additional methods to obtain the desired increase in SAM synthetase activity (i.e., a factor of 2 or more) beyond using a strong promoter or increasing the copy number of the gene of interest. With regard to methods to secrete SAM from *E. coli*, it is reiterated herein that the claims encompass unknown secretion mechanisms for SAM in bacterial cells, including *E. coli*. As previously indicated, the specification teaches that there is no SAM transport system in *E. coli* or other bacterial strains (page 4, last paragraph). Post-filing art by Tucker et al. disclose the first bacterial (*R. prowazekii*) AdoMet (SAM) transporter. Since neither the specification nor the art provide a teaching as to how to achieve secretion of

SAM in *E. coli* cells, one cannot reasonably conclude that secretion of SAM is adequately described. Therefore, for the reasons set forth above and those extensively discussed in the prior Office action, one of skill in the art cannot reasonably conclude that the teachings of the specification provide adequate description of the claimed method.

12. Claims 1-4 and 8-18 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the production of S-adenosylmethionine (SAM) comprising the steps of (1) culturing an *E. coli* cell modified such that the enzymatic activity of the *E. coli* SAM synthetase of SEQ ID NO: 1 is increased by transforming said *E. coli* cell with a plasmid that comprises a nucleic acid encoding the polypeptide of SEQ ID NO: 1 linked to an inducible promoter, and (2) recovering said SAM, does not reasonably provide enablement for a method for the production of SAM comprising the steps of (1) culturing a *Escherichia coli* strain, modified by any means such that the enzymatic activity of any SAM synthetase is increased by at least a factor of 2, and (2) secreting SAM to the culture medium. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

13. This rejection has been discussed at length in the Non Final action mailed on 9/26/2006 and is maintained for the reasons of record and those set forth below.

14. In addition to the arguments summarized above regarding the written description rejection, Applicant cites the Wands factors and provides specific reasons as to why no undue experimentation is required to make the present invention, namely (1) SAM synthetases are well known in the art and overproduction of SAM in *E. coli* is known in the art, (2) the specification provides exact guidance, fermentation of *E. coli* is known in the art, and organisms that overproduce SAM synthetase are well known in the art, (2) the examples shown in the specification shows how the invention works, (4)

fermentation processes are well known in the art, (5) the prior art teaches nearly all parts of the present invention except secretion of SAM, (6) the mutation of an enzyme and transformation of microorganisms is well known in the art, (7) it was not predictable that an *E. coli* with an increase SAM synthetase activity secretes SAM into the culture medium but if an *E. coli* strain with increased SAM synthetase activity secretes SAM into the culture medium, it is obvious that any *E. coli* strain overproducing any SAM synthetase would also secrete SAM into the medium, (8) amended claim 1 is limited to *E. coli*, SAM synthetase, and a specific amount of overexpression.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. The Examiner acknowledges the examples of the specification and the amendments made to claim 1. The Examiner also agrees that (1) overproduction of *E. coli* and rat liver SAM synthetases in *E. coli* has been disclosed in the prior art (see, for example, Art of Interest section of previous Office action), (2) fermentation and transformation of *E. coli* is well known in the art, (3) certain techniques are known in the art which would result in structural modification and/or overproduction of an enzyme, (4) enzymatic assays are known in the art, and (5) the prior art teaches all of the invention except for secretion of SAM into the culture medium. However the Examiner disagrees with Applicant's contention that the full scope of the claimed invention is enabled by the teachings of the specification and the prior art. The scope of the claims as amended has been described above. As indicated previously, the claims require 3 essential elements, (1) any enzymatically active SAM synthetase, (2) secretion of SAM from *E. coli*, and (3) increase in SAM synthetase activity such that the enzymatic activity is at least double that of the unmodified *E. coli*. These specific elements of the claimed invention are not fully enabled by the teachings of the specification in view of the fact that neither the specification nor the art disclose (1) the structure of all the SAM synthetases required by the claimed method, or how to obtain all the recited SAM synthetases, (2) how to secrete SAM from *E. coli*, and (3) how to achieve the specific level of SAM synthetase activity required beyond overexpression of a polynucleotide encoding the SAM

synthetase by increasing its copy number or by using a strong heterologous promoter. As stated in the Non Final action, the claims do not limit the method to achieve the recited enzymatic activity levels, thus the claims encompass a variety of methods such as the use of enhancers of SAM synthetase activity, mutations which would result in increased enzymatic activity, or transcription enhancers of any gene encoding a SAM synthetase. None of these methods have been disclosed.

With regard to secretion of SAM from *E. coli*, it is noted that as known in the art, the term "secretion" implies transport across a viable cellular membrane. The specification discloses the presence of SAM in the culture medium at 24 and 48 hours after induction without providing any evidence which would suggest that the presence of SAM in the culture medium is the result of transport from the cytoplasm to the culture medium (i.e., secretion). As previously indicated, one of skill in the art could reasonably conclude that Applicant's observations regarding the presence of SAM in the culture medium are the result of cell lysis. This is relevant due to the fact that, as indicated above, the specification teaches that there is no SAM transport system in *E. coli* or other bacterial strains (page 4, last paragraph). There is no post-filing reference teaching the discovery of a SAM transport mechanism in *E. coli*. The examples provided by Applicant do not indicate the use of an exogenous transport mechanism in *E. coli* that would secrete SAM, or the discovery of an endogenous secretion mechanism in *E. coli*. Thus, in view of the teachings of the specification and those of the art, one of skill in the art cannot reasonably conclude that the specification teaches a method wherein SAM is secreted from *E. coli* into the culture medium.

With regard to arguments that if an *E. coli* strain with increased SAM synthetase activity secretes SAM into the culture medium, it is obvious that any *E. coli* strain overproducing any SAM synthetase would also secrete SAM into the medium, the Examiner is not contending that overproduction of SAM synthetase in *E. coli* would not result in an increase in SAM, or that one could not overproduce known SAM synthetases in *E. coli* and reasonably expect an increase in SAM. Instead, the Examiner has

deemed the full scope of the claimed invention not to be enabled in view of the fact that (1) the specification does not teach how to secrete SAM from *E. coli*, (2) there is no information as to how to obtain all the SAM synthetases encompassed by the claims without undue experimentation, and (3) there is no teaching as to other methods to obtain the desired SAM synthetase activity beyond increasing the copy number of a polynucleotide encoding the SAM synthetase, or by placing said polynucleotide under the control of a strong heterologous promoter.

As extensively discussed in the previous Office action, it was not routine in the art to screen by a trial and error process for all proteins to determine which ones have SAM synthetase activity. Instead, one of skill in the art would have required some knowledge or guidance as to how structure correlates with the recited enzymatic function to determine which proteins comprise structural elements most likely to be associated with the recited function to limit the amount of experimentation to a reasonable number of species. In addition, it was not routine in the art to screen by trial and error for (1) essentially an infinite number of mutations in either the regulatory region of a gene or in the coding region of a gene to determine which ones result in increased SAM synthetase activity, as recited in the claims, (2) all possible enhancers of SAM synthetase activity such as chemicals and the products of other genes, (3) all possible transcription enhancers of genes encoding SAM synthetases such as chemicals and the products of other genes, or (4) all SAM transport proteins which would be active in an *E. coli* strain. In the absence of some knowledge or guidance as to (1) a structure/function correlation, (2) the structural variability within SAM synthetases, (3) changes within any SAM synthetase that would result in an increase of enzymatic activity, (4) changes within the regulatory elements of any gene encoding a SAM synthetase such that the synthesis of the gene products can be increased, (5) the structure of enhancers of the required enzymatic activity, (6) the structure of molecules capable of enhancing transcription of genes encoding SAM synthetases, and (7) SAM secretion mechanisms which would allow transfer of SAM from the cytoplasm to the medium, one of skill in the art would have to test an essentially infinite number of

proteins/compounds to determine which ones have SAM synthetase activity, enhance SAM synthetase activity, enhance transcription of SAM synthetase genes, and transport SAM to the extracellular medium. Therefore, for the reasons set forth above and those of record, one cannot reasonably conclude that the full scope of the claimed invention is enabled by the teachings of the specification and/or the art.

Conclusion

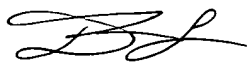
16. No claim is in condition for allowance.

17. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.



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DR
March 7, 2007

DELIA M. RAMIREZ, PH.D.
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